New Evidence for the Intermediacy of Spiroindolenines in the Bischler–Napieralski Cyclization of N_β-Acyltryptamines

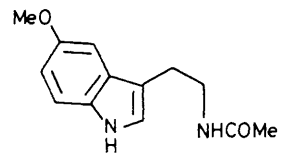
Jonathan R. Frost,*[a] Bernard R. P. Gaudillière,[a] and Alexander E. Wick[b]

L.E.R.S.-Synthélabo, Department of Chemistry, [a] 31, Av. P. Vaillant Couturier, 92220 Bagneux and [b] 58, Rue de la Glacière, 75013 Paris, France

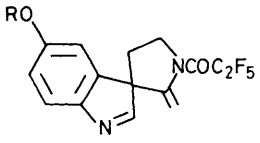
The isolation of novel polycyclic products (**7**), (**8**), and (**9**) from the Bischler–Napieralski cyclization of various N_β-acyltryptamines provides further evidence for the intermediacy of spiroindolenines in this reaction.

Mainly through the excellent work of Jackson *et al.*[1] it is well established that spirocyclic compounds are intermediates in the Pictet–Spengler synthesis of tetrahydro-β-carbolines from tryptamines and aldehydes. Only a few publications document the existence of an analogous reaction pathway in the Bischler–Napieralski cyclization of N_β-acylated tryptamines.

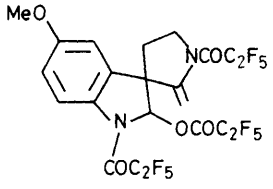
In 1977 Blau *et al.*[2] claimed that the structure of the compound formed by heating melatonin (**1**) in an excess of pentafluoropropionic anhydride was not the expected N_α-acylated dihydro-β-carboline[3] but the N_β-acylated indolenine (**2a**). Analogously, serotonin upon treatment with the anhydride of a carboxylic acid, followed by heating in pentafluoro-



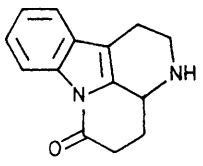
(1)



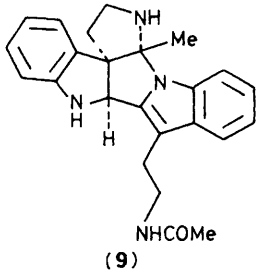
(2)
a; R = Me
b; R = COC_2F_5



(3)



(4)

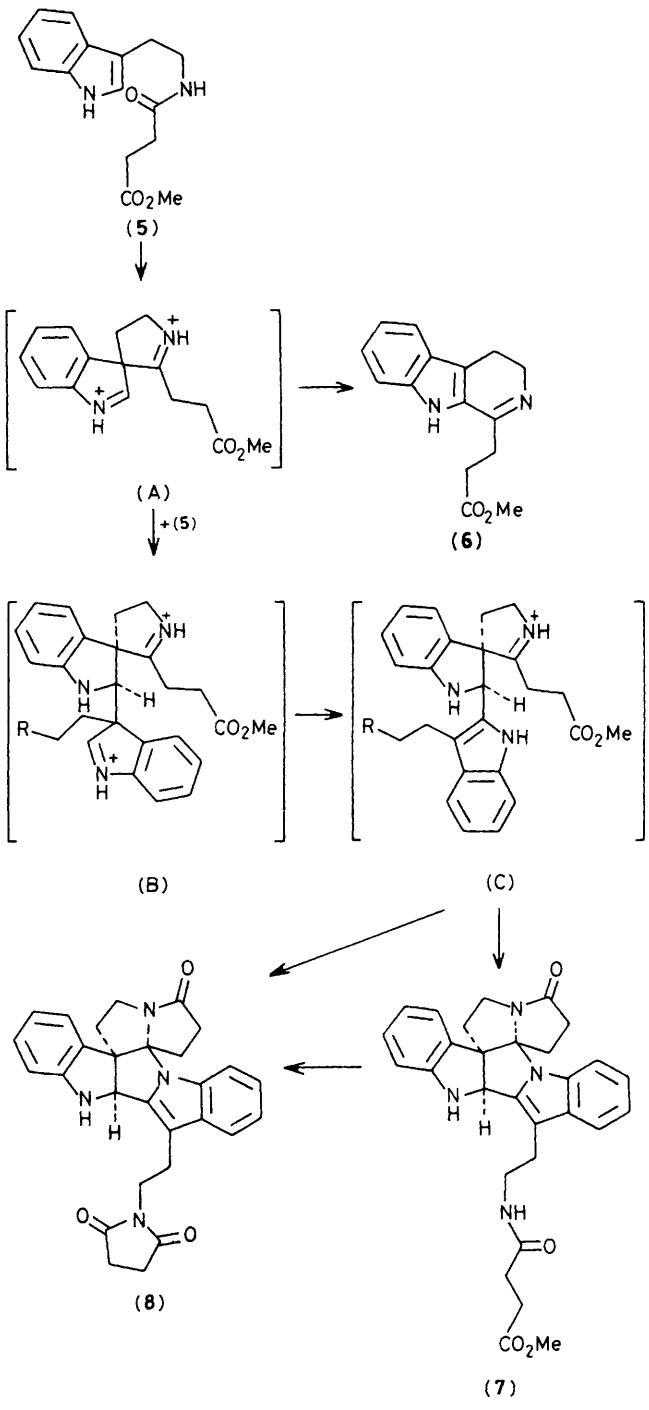


(9)

propionic anhydride was reported to give (**2b**).[4] However, Jackson *et al.*,[5] in repeating the work of Blau[2] and by providing n.m.r. and microanalytical support, proved beyond doubt that the compound obtained from melatonin was indeed the spiroindoline (**3**) and not the indolenine (**2a**). Two further reports[6,7] describe the intramolecular trapping of spiroindolenines. These reports thus constitute the first direct evidence for the close mechanistic analogy between the Pictet–Spengler and the Bischler–Napieralski reaction involving indole derivatives.

Recently, we explored synthetic routes to hexahydrocanthinones, *e.g.* (**4**), in which the Bischler–Napieralski reaction was to play a central role. When the tryptamine derivative (**5**) was treated in acetonitrile with a 10% excess of $POCl_3$ for one hour at 60 °C, the formation of the expected dihydro-β-carboline (**6**) could be observed, albeit in low yield (15%). The major reaction products, isolated in pure form by column chromatography and extensively characterized, were the two novel fused heptacyclic products (**7**) (28.5%, m.p. 113—115 °C, *m/z* 498) and (**8**) (25.2%, m.p. 238—239 °C, *m/z* 466).†

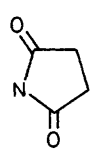
A plausible mechanism for the formation of (**7**) and (**8**) is depicted by structures (A)—(C). The stereochemistry of (**8**) was determined by *X*-ray crystallography‡ and is controlled by



(5)
(A)
(6)
(B)
(C)
(8)
(7)

R = $NHCO[CH_2]_2CO_2Me$

R =



the marked difference in steric hindrance that the substituted spiropyrroline in (A) exerts on the attacking indole species, *e.g.* (**5**). The relative stereochemistry of the third chiral centre

† Satisfactory microanalytical and spectral data were obtained for all new compounds.

‡ *Crystal data* for (**8**): $C_{28}H_{26}N_4O_3$, M = 466.53; orthorhombic, space group *Pbca*, U = 4597 Å^3, a = 19.165(3), b = 17.443(3), c = 13.752(2) Å, Z = 8, D_c = 1.35 g cm^{-3}. Data were measured with a Philips PW1100 diffractometer using the ω–2θ scan technique with graphite monochromated Cu-K_α radiation (λ = 1.5418 Å). The structure was solved by direct methods. The least-squares refinement based on 2357 observed reflections, with anisotropic temperature factors for the non-hydrogen atoms resulted in an R factor of 0.061. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

is a consequence of the stereoelectronic situation in (C). Compound (**7**), by short exposure to KOH in methanol, was easily transformed into (**8**).

In order to check the generality of the formation of the above described dimeric products through the intermolecular trapping of a spiroindolenine intermediate by unconsumed indole species, we treated N_{β}-acetyltryptamine in acetonitrile with a 10% excess of $POCl_3$. While the known 1-methyl-3,4-dihydro-β-carboline was formed together with other non-identified products, the fused hexacyclic compound (**9**) could be isolated as an amorphous solid in pure form (*m/z* 386). The stereochemistry of (**9**) has been assigned on the basis of the close similarity of relevant spectral data with those of (**7**) and (**8**).

The formation of (**7**), (**8**), and (**9**) adds to the existing evidence that the Bischler–Napieralski cyclisation of N_{β}-acyltryptamines involves initial reaction at the indole 3-position giving rise to a spirocyclic intermediate.

We thank Professor E. Wenkert for stimulating discussions and Dr. B. Mompon, L.E.R.S., for physico-chemical support.

Received, 5th March 1985; Com. 294

References

1 A. H. Jackson and P. Smith, *Tetrahedron*, 1968, **24**, 2227. For a review, see: F. Ungemach and J. M. Cook, *Heterocycles*, 1978, **9**, 1089.
2 K. Blau, G. S. King, and M. Sandler, *Biomed. Mass Spectrom.*, 1977, **4**, 232.
3 F. Cattabeni, S. H. Koslow, and E. Costa, *Science*, 1972, **178**, 166.
4 S. P. Markey, R. W. Colburn, and J. N. Johannessen, *Biomed. Mass Spectrom.*, 1981, **8**, 301.
5 K. M. Biswas, A. H. Jackson, and M. Tehrani, *J. Chem. Soc., Chem. Commun.*, 1982, 765.
6 J. C. Gaignault, D. Fréchet, and L. Nédelec, *Ann. Pharm. Fr.*, 1978, **36**, 401.
7 K. M. Biswas and A. H. Jackson, *J. Chem. Soc., Chem. Commun.*, 1983, 85.